JACC Vol. 20, No. 7
December 1992:1524–32

Diastolic Function of the Nonfilling Human Left Ventricle

WALTER J. PAULUS, MD, PhD, PASCAL J. VANTRIMPONT, MD,
MICHEL F. ROUSSEAU, MD, PhD, FACC*

Aalst, Belgium

Objectives. To investigate an early-diastolic left ventricular suction effect in humans, tip-micromanometer left ventricular pressure recordings were obtained in patients with mitral stenosis at the time of balloon inflations during percutaneous mitral valvuloplasty performed with a self-positioning Inoue balloon, which fits tightly in the mitral orifice.

Background. When mitral inflow was impeded in anesthetized dogs, left ventricular pressure decayed to a negative asymptote value. This negative asymptote value was consistent with an early diastolic suction effect.

Methods. Tip-micromanometer left ventricular pressure recordings were obtained in 23 patients with symptomatic mitral stenosis at the time of balloon inflations during percutaneous mitral valvuloplasty performed with a self-positioning Inoue balloon.

Results. The left ventricular diastolic asymptote pressure (P_{asy}) was determined in 47 nonfilling beats with a sufficiently long (>200 ms) diastolic time interval (that is, the interval from minimal first derivative of left ventricular pressure to left ventricular end-diastolic pressure) and equaled 2 ± 3 mm Hg for beats with normal intraventricular conduction and 3 ± 2 mm Hg for beats with aberrant intraventricular conduction. Left ventricular angiography was performed in five patients during the first inflation of the Inoue balloon at the time of complete balloon expansion. Left ventricular end-diastolic volume of the nonfilling beats averaged 38 ± 14 ml and was comparable to the left ventricular end-systolic volume (39 ± 19 ml) measured during baseline angiography before mitral valvuloplasty. Time constants of left ventricular pressure decay were calculated on 21 nonfilling beats with a diastolic time interval >200 ms, normal intraventricular conduction and peak left ventricular pressure >50 mm Hg. Time constants (T_0 and T_{BF}) derived from an exponential curve fit with zero asymptote pressure and with a best-fit asymptote pressure were compared with a time constant (T_{asy}) derived from an exponential curve fit with the measured diastolic left ventricular asymptote pressure. The value for T_{asy} (37 ± 9 ms) was significantly smaller than that for T_{BF} (68 ± 28 ms, $p < 0.001$) and the value for the measured diastolic left ventricular asymptote pressure (2 ± 4 mm Hg) was significantly larger than that for the best-fit asymptote pressure (−9 ± 11 mm Hg, $p < 0.001$). T_0 (44 ± 20 ms) was significantly ($p < 0.01$) different from T_{BF} but not from T_{asy}.

Conclusions. During balloon inflation of a self-positioning Inoue balloon, left ventricular pressure decayed continuously toward a positive asymptote value and left ventricular cavity volume was comparable to the left ventricular end-systolic volume of filling beats. In these nonfilling beats, the best-fit asymptote pressure was unrelated to the measured asymptote pressure and T_0 was a better measure of T_{asy} than was T_{BF}. Reduced internal myocardial restoring forces, caused by different extracellular matrix of the human heart, reduced external myocardial restoring forces caused by low coronary perfusion pressure during the balloon inflation and inward motion of the balloon-occluded mitral valve into the left ventricular cavity could explain the failure to observe significant diastolic left ventricular suction in the human heart.

(J Am Coll Cardiol 1992;20:1524–32)

Left ventricular pressure decay in the absence of left ventricular inflow has been analyzed in anesthetized open chest dogs by using a mitral anulus occluder (1). These experiments revealed continuous exponential decay of left ventricular pressure toward a negative asymptote value in the range of −5 to −8 mm Hg. This negative asymptote value of left ventricular pressure decay in the absence of left ventricular inflow confirmed the existence of an early diastolic left ventricular suction effect (2,3). This effect is thought to originate from myocardial restoring forces (4), which induce early diastolic outward motion of the left ventricular wall. When this early diastolic increase in left ventricular volume proceeds faster than early diastolic left ventricular inflow, a suction effect is created and early diastolic left ventricular pressure becomes negative. Negative early diastolic left ventricular pressure was also observed in patients with obstructed left ventricular inflow due to mitral stenosis (5) and recently in normal subjects during infusion of isoproterenol, which augments left ventricular restoring forces probably because of a small end-systolic left ventricular cavity size (6).

This negative asymptote value of left ventricular pressure

From the Cardiovascular Center, O. L.V. Ziekenhuis, Aalst and *Division of Cardiology, University of Louvain, Brussels, Belgium. This study was presented in part at the 64th Scientific Sessions of the American Heart Association, Anaheim, California, November 1991.

Manuscript received March 11, 1992; revised manuscript received May 23, 1992, accepted June 27, 1992.

Address for correspondence: Walter J. Paulus, MD, PhD, Cardiovascular Center, O. L.V. Ziekenhuis, Moorselbaan 164, B 9300 Aalst, Belgium.

0735-1097/92/$5.00

Table 1. Patient Characteristics and Effects of Balloon Mitral Valvuloplasty on Mitral Valve Area and Left Ventricular Minimal Diastolic Pressure

				Mitral Valve Area		LVMDP	
Pt No.	Age (yr)/ Gender	LVEDVI (ml/m²)	LVEF (%)	Pre (cm²)	Post (cm²)	Pre (mm Hg)	Post (mm Hg)
1	46/M	81	75	1.4	2.2	1	2
2	51/F	88	53	1.2	2.2	−1	1
3	39/F	81	61	0.7	2.0	0	1
4	32/M	119	64	1.1	2.3	−3	5
5	70/F	76	63	1.5	2.1	3	6
6	62/F	31	67	1.2	2.9	1	2
7	47/F	86	50	1.0	2.2	7	7
8	74/F	47	66	1.2	2.0	4	5
9	52/F	76	66	1.5	2.6	6	3
10	54/F	12[illegible]	63	1.0	1.8	10	8
11	56/F	62	68	1.2	2.1	2	2
12	41/F	69	76	1.1	2.6	0	0
13	65/F	69	83	1.2	2.1	2	0
14	69/M	91	67	0.9	1.9	2	5
15	47/F	80	81	1.2	2.0	−1	1
16	71/F	57	64	0.7	1.4	1	3
17	54/F	56	57	1.2	2.3	1	4
18	53/M	86	75	1.0	1.8	0	4
19	51/F	70	62	1.2	2.3	2	6
20	36/M	97	58	1.5	2.1	3	2
21	55/M	81	78	1.5	2.9	2	2
22	47/F	66	58	0.9	1.5	5	12
23	46/F	61	57	0.8	2.0	4	3
Mean	53	76	66	1.1	2.1*	2	4†
±SD	11	21	9	0.2	0.4	3	3

*$p < 0.001$. †$p < 0.02$. F = female; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVMDP = left ventricular minimal diastolic pressure; M = male; Post = after valvuloplasty; Pre = before valvuloplasty; Pt = patient.

decay in the absence of left ventricular inflow favored the use of an exponential curve fit with a non-zero asymptote pressure to calculate the time constant of isovolumetric left ventricular pressure decay (7–9) instead of the previously proposed (10) exponential curve fit with zero asymptote pressure. However, in the anesthetized open chest dog with a mitral anulus occluder the measured diastolic left ventricular asymptote pressure of nonfilling beats was significantly different from the non-zero asymptote pressure derived from the best exponential curve fit to isovolumetric left ventricular pressure decay (1). This experimental finding suggested best-fit asymptote pressure to be unrelated to the true diastolic left ventricular asymptote pressure. A similar conclusion was suggested by the unrealistically large negative values of best-fit asymptote pressure in the range of −20 mm Hg observed in patients with aortic stenosis (11–13) and by the failure of best-fit asymptote pressure to become more negative during exercise (9).

In the present study, diastolic left ventricular pressure decay was analyzed in patients with symptomatic mitral stenosis at the time of percutaneous transseptal mitral valvuloplasty during inflation of a self-positioning Inoue balloon that fit tightly in the mitral orifice (14). The following issues were addressed: 1) confirmation of the absence of left ventricular filling during inflation of the Inoue balloon by simultaneous left ventricular angiography; 2) measurement of the diastolic left ventricular asymptote pressure in nonfilling beats; and 3) comparison of the measured diastolic left ventricular asymptote pressure and the calculated best-fit asymptote pressure value in nonfilling beats.

Methods

Study patients. Tip-micromanometer left ventricular pressure recordings were obtained in 23 patients (17 women and 6 men; age range 32 to 74 years [mean age 53 ± 11]) during balloon inflation at the time of percutaneous transseptal mitral valvuloplasty performed with a self-positioning Inoue balloon. All patients were referred for valvuloplasty because of symptomatic rheumatic mitral stenosis and echocardiographic features of the mitral valve that were favorable for treatment with balloon mitral commissurotomy (15). No patient had significant concomitant aortic or tricuspid valve disease or >2+ mitral regurgitation on the left ventricular angiogram obtained before the procedure. Table 1 lists individual patient characteristics, left ventricular end-

JACC Vol. 20, No. 7
December 1992:1524–32

diastolic volume index, left ventricular ejection fraction, mitral valve area before and after balloon mitral valvuloplasty and left ventricular minimal diastolic pressure before and after valvuloplasty. Mitral valve area was calculated with the Gorlin formula (16). Angiographic left ventricular indexes were calculated from single-plane left ventricular angiograms performed in the 30° right anterior oblique projection (17). Baseline left ventricular end-diastolic volume index and baseline left ventricular ejection fraction were, respectively, 76 ± 21 ml/m^2 and 66 ± 9%. After valvuloplasty, mitral valve area increased from 1.1 ± 0.2 to 2.1 ± 0.4 cm^2. There were no immediate or late complications as a result of the procedure except for an increase in mitral regurgitation by one angiographic grade in two patients.

Procedure. Diagnostic left and right heart catheterization was performed before the balloon mitral valvuloplasty procedure with use of the left femoral artery and vein. All pressures were referenced to atmospheric pressure at the level of the midchest. Cardiac output was measured with Fick or thermodilution techniques (average of at least three values; 9520A Cardiac Output Computer, Edwards Laboratories). Left ventricular pressure was measured with a tip-micromanometer left ventricular pressure catheter calibrated externally against a mercury reference and matched against lumen pressure. A first derivative of left ventricular pressure (dP/dt) signal was obtained by an electronic differentiator. After prevalvuloplasty hemodynamic measurements, transseptal puncture was performed from the right femoral vein and the transseptal catheter was subsequently exchanged for the self-positioning Inoue balloon. Inoue balloon size was determined by patient height (14). Left ventricular pressure, left ventricular dP/dt, a cine frame marker and a bipolar standard lead of the electrocardiogram (ECG) were recorded on a Gould ES 1000 multichannel recorder during balloon inflation. A biplane left ventricular angiogram was performed during the first balloon inflation in five patients. After balloon valvuloplasty, hemodynamic measurements and left ventricular angiography were repeated.

Data analysis. All hemodynamic data (Table 1) were averaged over a complete respiratory cycle. Pressure signals were digitized on line with a Hewlett-Packard 9836 computer. The left ventricular diastolic asymptote pressure was determined at the time of inflation of the self-positioning Inoue balloon during the nonfilling beats with a sufficiently long (>200 ms) diastolic time interval. The diastolic time interval was defined as the interval between minimal left ventricular dP/dt and the onset of the QRS complex of the following beat. Left ventricular diastolic asymptote pressure was measured at the onset of the QRS complex of the following beat. Nonfilling beats with a sufficiently long diastole (n = 47) were observed in 15 of the 23 patients (Table 2) in whom tip-micromanometer left ventricular pressure recordings were obtained during balloon commissurotomy. The left ventricular diastolic asymptote pressure and

Table 2. Left Ventricular Diastolic Asymptote Pressure (P_{asy}) and Diastolic Time Interval (DTI) of Nonfilling Beats With a Diastolic Time Interval >200 ms

Pt No.	Normally Conducted Beats		Aberrantly Conducted Beats	
	P_{asy} (mm Hg)	DTI (ms)	P_{asy} (mm Hg)	DTI (ms)
1	0	528		
	0	328		
	1	208		
	2	204		
	−3	204		
	−3	288		
	0	252		
	3	216		
2	−2	328		
	−2	328		
6	7	276		
	7	326		
	5	276		
	0	252		
	−1	280		
7			7	368
8	3	616		
9			4	252
10	3	440	1	432
11	4	508	2	708
	5	768		
12	4	494		
	4	248		
	6	288		
	4	280		
	5	280		
	7	280		
13	0	322		
	0	382		
	−1	275		
	2	300		
14			6	825
16			3	225
			0	245
			3	285
			−1	482
17	−3	315	3	255
			3	300
21	2	484		
	−2	488		
	−3	484		
23			4	468
			0	244
			2	868
Mean	2	350	3	426
±SD	3	131	2	223

Pt = patient.

diastolic time interval values for the individual nonfilling beats with a diastolic time interval >200 ms (n = 47) are shown in Table 2. Of these 47 nonfilling beats, 21 were considered suitable for calculation of time constants of left ventricular pressure decay. These 21 nonfilling beats (Table 3) fulfilled the additional criteria of normal intraventricular conduction and peak left ventricular pressure >50 mm Hg.

Table 3. Time Constants of Isovolumetric Left Ventricular Pressure Decay of Nonfilling Normally Conducted Beats With Peak Left Ventricular Pressure >50 mm Hg and Diastolic Time Interval >200 ms

Pt No.	LVPSP (mm Hg)	IVRT (ms)	T_{asy} (ms)	P_{asy} (mm Hg)	r_{asy}	T_0 (ms)	r_0	T_{BF} (ms)	P_{BF} (mm Hg)	r_{BF}
1	79	34	24	0	0.996	24	0.996	42	−7	0.999
	61	60	37	0	0.989	37	0.989	121	−30	0.999
	67	65	38	1	0.997	42	0.998	54	−4	0.999
	66	58	37	2	0.995	43	0.997	65	−8	0.999
	66	65	39	−3	0.998	29	0.991	53	−8	0.999
	64	50	31	−3	0.983	22	0.960	97	−30	0.998
	65	51	31	3	0.995	39	0.998	59	−8	0.999
	64	42	29	0	0.985	29	0.985	104	−30	0.999
2	56	55	37	−2	0.998	29	0.997	37	−2	0.998
	50	46	37	−2	0.999	30	0.997	41	−3	0.999
6	63	50	30	7	0.998	57	0.997	37	6	0.999
	60	63	44	7	0.999	74	0.996	44	7	0.999
12	56	51	32	4	0.996	42	0.999	48	−2	0.999
	53	87	55	4	0.993	72	0.998	116	−11	0.999
	57	90	48	6	0.997	73	0.999	69	1	0.999
	58	113	57	4	0.999	75	0.998	62	3	0.999
	56	76	44	5	0.991	61	0.998	103	−13	0.999
	58	77	46	7	0.993	70	0.998	103	−10	0.999
21	88	51	26	2	0.987	29	0.991	72	−25	0.999
	63	31	26	−2	0.995	20	0.989	62	−16	0.999
	80	63	33	−3	0.998	24	0.988	41	−6	0.999
Mean	63	61	37	2	0.994	44	0.993	68*†	−9‡	0.999
±SD	9	19	9	4		20		28	11	

*$p < 0.001$ versus the time constant of isovolumetric left ventricular pressure decay derived from a curve fit with the diastolic asymptote pressure. †$p < 0.01$ versus the time constant of isovolumetric left ventricular pressure decay derived from a curve fit with a zero asymptote pressure. ‡$p < 0.001$ versus the left ventricular diastolic asymptote pressure. IVRT = isovolumetric relaxation time; LVPSP = left ventricular peak systolic pressure; P_{asy} = left ventricular diastolic asymptote pressure; P_{BF} = best-fit left ventricular asymptote pressure; Pt = patient; r_{asy} = correlation coefficient of the curve fit used to calculate the time constant of isovolumetric left ventricular pressure decay with the diastolic asymptote pressure; r_{BF} = correlation coefficient of the curve fit used to calculate the time constant of isovolumetric left ventricular pressure decay with the best fit asymptote pressure; r_0 = correlation coefficient of the curve fit used to calculate the time constant of isovolumetric left ventricular pressure decay with a zero asymptote pressure; T_{asy} = time constant of isovolumetric left ventricular pressure decay derived from a curve fit with the diastolic asymptote pressure; T_{BF} = time constant of isovolumetric left ventricular pressure decay derived from a curve fit with the best fit asymptote pressure; T_0 = time constant of isovolumetric left ventricular pressure decay derived from a curve fit with a zero asymptote pressure.

Pressure data points for these 21 beats were obtained at 1-ms intervals by digitizing the left ventricular pressure signal from the moment of minimal left ventricular dP/dt to a time at which left ventricular pressure had decayed to a value that equaled left ventricular diastolic asymptote pressure plus 5 mm Hg (Fig. 1). For each beat, three different time constants (T_{asy}, T_0 and T_{BF}) of left ventricular pressure decay were derived from three different exponential curve fits to the digitized left ventricular pressure data points (Table 3). The value for T_{asy} was calculated from a monoexponential curve fit with the diastolic asymptote pressure (P_{asy}):

$$P = (P_0 - P_{asy})e^{(-t/T_{asy})} + P_{asy},$$

where P_0 is left ventricular pressure at the moment of minimal left ventricular dP/dt and t is time. The value for T_0 was calculated from a monoexponential curve fit with zero asymptote pressure by the method of Weiss et al. (10):

$$P = P_0e^{(-t/T_0)}.$$

Finally, T_{BF} was calculated from a monoexponential curve fit with an asymptote pressure (P_{BF}) that yielded the best fit to the digitized left ventricular pressure data points by the variable asymptote pressure method (7–9):

$$P = (P_0 - P_{BF})e^{(-t/T_{BF})} + P_{BF}.$$

Left ventricular angiography was performed during the first inflation of the self-positioning Inoue balloon in five patients with use of 10 ml of ioxaglate at a flow rate of 10 ml/s. Because of the absence of left ventricular filling, a small amount (10 ml) of contrast medium was sufficient to adequately opacify the left ventricular cavity during balloon inflation. In each patient in whom a contrast left ventricular angiogram was performed during balloon inflation, left ventricular end-diastolic volume was measured in a nonfilling beat with a diastolic time interval >200 ms. Nonfilling beats that occurred at the time of contrast medium injection were excluded for determination of P_{asy}.

Statistical analysis. Results are reported as mean value ± SD. The level of statistical significance was set at $p < 0.05$ and the probability value was obtained by the Student *t* test for paired data. For multiple comparisons, a Bonferroni *t* test was performed if analysis of variance yielded a statistically significant F value.

JACC Vol. 20, No. 7
December 1992:1524–32

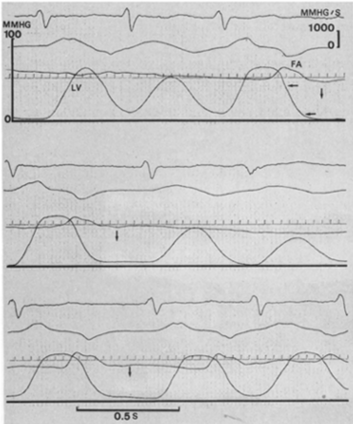

Figure 1. Tip-micromanometer left ventricular (LV) pressure recording during inflation of a self-positioning Inoue balloon in the mitral valve. The different recordings from top to bottom show a single lead electrocardiogram, first derivative of left ventricular pressure dP/dt, tip-micromanometer left ventricular pressure, femoral artery (FA) pressure and a cine frame marker. Complete balloon expansion is achieved at the upper left corner and balloon deflation starts at the lower right corner of the recording. Beats indicated with a vertical arrow were used for measurement of left ventricular diastolic asymptote pressure because of sufficient length of diastole. The upper and lower horizontal arrows indicate, respectively, the starting point and end point of that portion of the left ventricular pressure signal that was digitized to calculate the time constants (T_{asy}, T_0 and T_{BF}) of left ventricular pressure decay.

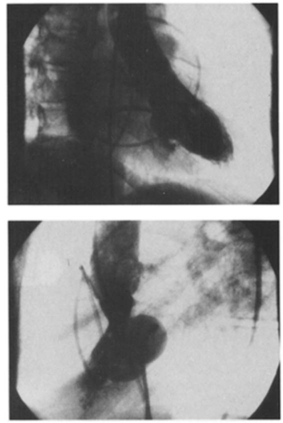

Figure 2. Biplane (30° right anterior oblique and left lateral) left ventricular angiograms performed during inflation of the Inoue valvuloplasty balloon.

Results

Left ventricular diastolic asymptote pressure and left ventricular end-diastolic volume of nonfilling beats. A tip-micromanometer left ventricular pressure recording obtained during inflation of a self-positioning Inoue balloon is shown in Figure 1. The left ventricular diastolic asymptote pressure was determined in the nonfilling beats with a sufficiently long (>200 ms) diastolic time interval (Table 2). A diastolic time interval of 200 ms corresponds to 5.4 times the time constant of left ventricular pressure decay derived from an exponential curve fit with the diastolic left ventricular asymptote pressure (T_{asy}). This diastolic time interval allows for an exponential left ventricular pressure decay to a value lower than $P_0/200$ (where P_0 = left ventricular pressure at the moment of minimal left ventricular dP/dt). Forty-seven nonfilling beats with a sufficiently long diastole were observed in 15 patients. The individual values of the diastolic time interval and diastolic asymptote pressure for these 47 beats are listed in Table 2. For the 33 beats with normal intraventricular conduction, the diastolic time interval was 350 ± 131 ms and left ventricular diastolic asymptote pressure was 2 ± 3 mm Hg. For the 14 beats with aberrant intraventricular conduction, the diastolic time interval was 426 ± 223 ms and left ventricular diastolic asymptote pressure was 3 ± 2 mm Hg.

Left ventricular angiography during inflation of the self-positioning Inoue balloon was performed in five patients at the time of complete balloon expansion (Fig. 2). Entry of unopacified blood into the left ventricular cavity could not be detected on these left ventricular angiograms. This observation was consistent with obstruction of left ventricular inflow by the inflated balloon. In each patient, left ventricular end-diastolic volume was measured in a nonfilling beat with a diastolic time interval >200 ms. Left ventricular end-diastolic volume of the nonfilling left ventricle was 38 ± 14 ml and was not significantly different from the volume (39 ± 19 ml) observed in these five patients at the time of the baseline left ventricular angiogram.

Effect of balloon mitral valvuloplasty on left ventricular minimal diastolic pressure. Left ventricular minimal diastolic pressure increased from 2 ± 3 mm Hg before to 4 ± 3 mm Hg after balloon mitral valvuloplasty ($p < 0.02$) (Table 1). Negative left ventricular minimal diastolic pressures were observed before balloon mitral valvuloplasty in 3 of the 23

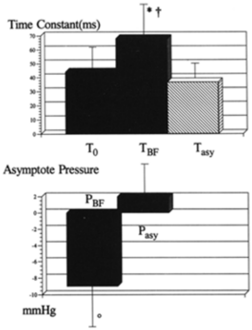

Figure 3. Values of the time constants of left ventricular pressure decay calculated in the nonfilling beats using a zero asymptote pressure (T_0), a best fit asymptote pressure (T_{BF}) and the measured diastolic left ventricular asymptote pressure (T_{asy}) (**top panel**) and the values of the best fit asymptote pressure (P_{BF}) and the measured diastolic left ventricular asymptote pressure (P_{asy}) (**bottom panel**). *$p < 0.001$ versus T_{asy}; †$p < 0.01$ versus T_0; °$p < 0.001$ versus P_{asy}.

patients in whom tip-micromanometer left ventricular pressure recordings were obtained (Table 1). In these three patients, left ventricular minimal diastolic pressure became positive after balloon mitral valvuloplasty.

Time constant of isovolumetric left ventricular pressure decay: assessment in the nonfilling human left ventricle. Time constants of left ventricular pressure decay were calculated in 21 nonfilling beats (Table 3) that fulfilled the criteria of a diastolic time interval >200 ms, normal intraventricular conduction and peak left ventricular pressure >50 mm Hg. For each beat, three different time constants (T_{asy}, T_0 and T_{BF}) of left ventricular pressure decay were calculated using three different exponential curve fits to the digitized left ventricular pressure data points; T_{asy} was calculated from a monoexponential curve fit with the measured diastolic asymptote pressure, T_0 from a monoexponential curve fit with zero asymptote pressure and T_{BF} from a monoexponential curve fit with an asymptote pressure derived from a best fit to the digitized left ventricular pressure data points. For these 21 beats, left ventricular peak systolic pressure averaged 63 ± 9 mm Hg and left ventricular isovolumetric relaxation time 61 ± 9 ms. The value for T_{asy} (37 ± 9 ms) was significantly lower than that for T_{BF} (68 ± 28 ms; $p < 0.001$) and left ventricular diastolic asymptote pressure (2 ± 4 mm Hg) was significantly higher than best-fit asymptote pressure (−9 ± 11 mm Hg; $p < 0.001$). Finally, T_0 (44 ± 20 ms) was significantly ($p < 0.01$) different from T_{BF} but not from T_{asy} (Fig. 3).

Discussion

Nonfilling beats in the human heart. The time course of left ventricular isovolumetric relaxation in the absence of left ventricular inflow has been analyzed experimentally in an open chest anesthetized dog preparation by using a mitral anulus occluder (1). In the human left ventricle, left ventricular pressure decay in the absence of left ventricular filling has not been analyzed until now. During balloon inflations at the time of mitral valvuloplasty with the double-balloon technique, left ventricular inflow is only partially prevented because of open space in between the two cylindric balloons. During the inflation with the Inoue balloon technique, left ventricular inflow is obstructed at the time of complete balloon expansion because of the self-positioning effect of the dumbbell-shaped balloon in the mitral orifice. This obstruction of the left ventricular inflow was evident on the left ventricular angiograms performed during balloon inflation. Balloon inflation therefore provides an opportunity to study left ventricular pressure decay in the absence of left ventricular filling in the human heart. During mitral valvuloplasty performed with the Inoue balloon technique, left ventricular pressure shows uninterrupted decay toward a positive asymptote pressure of 2 ± 3 mm Hg for the normally conducted beats and toward a positive asymptote pressure of 3 ± 2 mm Hg for the aberrantly conducted beats. These positive asymptote values are in contrast to the negative asymptote values previously reported (1) in anesthetized open chest dogs with obstructed mitral inflow. Because of average subatmospheric intrathoracic pressure in humans during regular breathing, transmural left ventricular pressure of the nonfilling beats would probably have an even higher positive value.

Discrepancy between experimental and clinical findings on diastolic left ventricular suction. *Theoretic considerations.* The negative diastolic left ventricular asymptote pressure observed in anesthetized dogs with obstructed mitral inflow has been attributed to diastolic left ventricular suction caused by internal restoring forces (1). These internal restoring forces result from compression of certain components of the extracellular matrix of the myocardium during systole (18) and their presence implies a contraction to a left ventricular end-systolic volume (19) that is smaller than the left ventricular equilibrium volume. Left ventricular equilibrium volume is defined as the volume of the ventricle at rest at zero transmural pressure. Its exact value has been controversial, ranging from 15 ml (20) to 37 ml (19) in the dog heart. This wide range of values prompted investigators to form opposite conclusions with respect to the relative importance of diastolic suction. Investigators (4,21) who observed a small left ventricular equilibrium volume attributed only a limited role to diastolic suction because the left ventricular end-systolic volume usually exceeded the left ventricular equilibrium volume. Conversely, investigators (19) who observed a large left ventricular equilibrium volume reported a frequent occurrence of diastolic left ventricular

JACC Vol. 20, No. 7
December 1992:1524–32

suction. The present study of diastolic left ventricular function under conditions of impeded left ventricular inflow was performed in conscious patients at rest, whereas previous experimental studies were performed in open chest anesthetized dogs. In these experiments, anesthesia and thoracotomy both contributed to a hyperadrenergic state, as evident from the increased rest heart rate (106 ± 17 beats/min in Ref 19). A hyperadrenergic state increases the likelihood of achieving an end-systolic left ventricular volume smaller than the left ventricular equilibrium volume. Moreover, a higher inotropic state also affects the magnitude of a diastolic left ventricular suction effect, as evident from the steeper slope of the negative portion of the diastolic left ventricular pressure-volume relation (19). The discrepancy between the findings in human and dog hearts could also be related to alterations of the composition of the extracellular matrix in the human heart (22–24) due to aging or previous rheumatic myocarditis. Evidence for myocarditis-induced alterations of the extracellular matrix was provided by reports of mitral stenosis with reduced diastolic left ventricular compliance (25) and with reduced left ventricular dilation in the presence of left ventricular volume overload due to concomitant aortic regurgitation (26). Moreover, a tethering effect of the inferobasal portion of the left ventricle to the mitral anulus (27), which is known to reduce inferobasal systolic inward motion, could also affect early diastolic left ventricular recoil of this segment.

Negative early diastolic left ventricular pressures such as those observed in patients with mitral stenosis, normal subjects during infusion of isoproterenol and anesthetized dogs after mitral valve occlusion have also been explained by external restoring forces (4), which are of a noncompressive nature and related to external loading of the myocardial fibers in early diastole (for example, by coronary perfusion pressure). Whenever this external loading on the fibers results in an outward wall motion faster than left ventricular inflow, negative intraventricular pressures are created. In the presence of mitral stenosis, left ventricular inflow is impeded and the speed of left ventricular outward wall motion can therefore exceed left ventricular inflow kinetics, leading to negative early diastolic left ventricular pressures as occasionally observed in the present and previous studies. During the balloon inflations in the present study, the magnitude of left ventricular external restoring forces is reduced compared with that reported in previous experiments in anesthetized dogs using a mitral valve occluder. In the present study, peak left ventricular pressure, and therefore aortic pressure and coronary perfusion pressure were lower than values in the anesthetized dog experiments because a continuous series of nonfilling beats was analyzed; in the previous experimental work, the nonfilling beat was the first beat after a series of regular filling beats. A lower coronary perfusion pressure reduces early diastolic left ventricular external restoring forces and could contribute to the absence of diastolic suction in the present observations. The importance of coronary perfusion pressure as a modulator of diastolic sarcomere stretch was recently reemphasized by comparing the early effects of myocardial ischemia in the microembolized and nonperfused isovolumetric rodent heart (28). Moreover, the low left ventricular systolic pressure that developed in the present study leads to early onset of left ventricular relaxation at a time when myocardial calcium reuptake could still be incomplete (13), thereby further reducing myocardial sensitivity to early diastolic external left ventricular restoring forces (4).

Methodologic considerations. The presence of the Inoue valvuloplasty balloon inside the left ventricular cavity could have interfered with diastolic recoil of the left ventricular wall. A fully inflated Inoue balloon of 30-mm diameter occupies ±15 ml of the subvalvular left ventricular cavity space, which is less than half of the angiographic left ventricular volume during balloon inflation. Substantial distension of the left ventricular wall by the inflated balloon therefore seems unlikely.

Occlusion of the native mitral valve by a balloon obstructs left ventricular inflow in a different manner from that of the mechanical occluder used in animal experiments. During balloon occlusion of the mitral valve, valve leaflets and mitral apparatus are pushed inside the left ventricular cavity by the increasing left atrial pressure. This motion is obvious on the left ventricular angiogram in Figure 2, which shows the mitral leaflets wrapped around the balloon and bulging inside the left ventricular cavity during balloon inflation. Such motion of the mitral leaflets into the left ventricular cavity could abolish a suction effect created by elastic recoil of the left ventricular wall. In animal experiments, larger subatmospheric pressures were indeed observed during episodes of obstructed left ventricular inflow when the mitral anulus occluder remained fixed in position (1) than when the native mitral valve was preserved (29). The motion of the leaflets into the left ventricular cavity observed in the present study during balloon inflation is consistent with relatively preserved valve mobility and pliability characteristic of patients referred for balloon mitral valvuloplasty (15). The relative preservation of valve mobility in these patients could explain the rare occurrence in the present study of negative early diastolic left ventricular pressures (3 of 23 patients) in contrast to previous reports (5). These previous reports were based on patients with mitral stenosis who were not specifically referred for balloon mitral valvuloplasty and probably had a higher incidence of fixed and amobile valves, which favor the creation of subatmospheric early diastolic left ventricular pressures.

Failure to observe diastolic suction in the human heart could be related to incomplete mitral orifice occlusion during Inoue balloon inflation. The following findings argue against major residual inflow through the mitral orifice during the balloon inflation: 1) the dumbbell shape of the balloon, which makes it fit tightly in the mitral orifice; 2) absence of negative filling defects on the left ventricular angiogram during balloon inflation; and 3) the presence of uninterrupted diastolic left ventricular pressure decay on the high fidelity tip-micromanometer left ventricular pressure signal. The experiments of Nikolic et al. (19) suggest that uninterrupted left ventricular pressure decay indicates no or limited early diastolic left ventricular inflow because these investigators found that partial left ventricular inflow resulted in a shift in the left ventricular pressure wave to an early diastolic pressure minimum followed by an upward curve.

Diastolic left ventricular viscous forces. In the present study, left ventricular minimal diastolic pressure showed a small but significant increase from 2 ± 3 mm Hg before valvuloplasty to 4 ± 3 mm Hg after valvuloplasty. In the absence of diastolic left ventricular suction and in the presence of comparable isovolumetric left ventricular relaxation rates (30), this finding is most likely the result of a viscous effect because of faster early diastolic left ventricular wall motion after relief of the mitral inflow obstruction. The small magnitude of the change in left ventricular minimal diastolic pressure (2 mm Hg) despite the drastic alteration in left ventricular inflow kinetics after valvuloplasty is consistent with a limited effect of viscous forces and with a predominant effect of decaying left ventricular relaxation on early diastolic left ventricular filling pressure (31).

Time constant of left ventricular pressure decay in nonfilling beats. A time constant derived from a monoexponential analysis of the isovolumetric portion of left ventricular pressure decay has been widely applied in both experimental and clinical studies (8–10) to characterize the isovolumetric left ventricular relaxation rate. The asymptote toward which left ventricular pressure decays has been the subject of controversy and led to the use of two different mathematic expressions to calculate the time constant of left ventricular pressure decay using either a zero asymptote pressure (10) or a variable asymptote pressure (7–9). The variable asymptote pressure was derived from a best fit procedure and its relation to the true left ventricular asymptote pressure in the absence of left ventricular filling was analyzed previously in anesthetized open chest dogs by Yellin et al. (1). Their results were similar to those in the present study and showed a significant difference between 1) the measured asymptote pressure of the nonfilling beats and the asymptote pressure calculated by a best fit procedure, and 2) the time constant calculated with the measured asymptote and the time constant derived by a best fit procedure. In both studies, large negative diastolic asymptote pressures (−18 ± 7 mm Hg in Ref 1; −9 ± 11 mm Hg in the present study) were calculated by a best fit procedure to the "isovolumetric" portion of left ventricular pressure decay. These calculated diastolic left ventricular asymptote pressures were much more negative than the measured diastolic left ventricular asymptote pressures because the terminal portion of left ventricular pressure decay proceeded faster than the initial portion. Because of this faster decay of the terminal portion, calculations assuming a zero asymptote pressure yielded a time constant that was closer to the value derived with the measured diastolic left ventricular asymptote pressure of the nonfilling beat. The present observations therefore support the use of a time constant with zero asymptote pressure to measure isovolumetric left ventricular relaxation kinetics in the human heart.

Conclusions. In the present study, a positive diastolic left ventricular asymptote pressure was observed in the human left ventricle when left ventricular inflow was obstructed with an inflated Inoue valvuloplasty balloon. This finding is in contrast to previous observations in anesthetized open chest dogs obtained with the use of a mechanical mitral anulus occluder. Reduced internal myocardial restoring forces due to the different extracellular matrix of the human heart, reduced external myocardial restoring forces caused by low arterial pressure during Inoue balloon inflation and inward motion of the balloon-occluded mitral valve could explain the absence of diastolic left ventricular suction in the human heart during Inoue balloon inflation.

References

1. Yellin EL, Hori M, Yoran C, Sonnenblick EH, Gabbay S, Frater RWM. Left ventricular relaxation in the filling and nonfilling intact canine heart. Am J Physiol 1986;250:H620–9.
2. Brecher GA. Experimental evidence of ventricular diastolic suction. Circ Res 1956;4:513–8.
3. Tyberg JV, Keon WJ, Sonnenblick EH, Urschel CW. Mechanics of ventricular diastole. Cardiovasc Res 1970;4:423–8.
4. Brutsaert DL, Rademakers FE, Sys SU. Triple control of relaxation: implications in cardiac disease. Circulation 1984;69:190–6.
5. Sabbah HN, Anbe DT, Stein PD. Negative intraventricular diastolic pressure in patients with mitral stenosis: evidence of left ventricular diastolic suction. Am J Cardiol 1980;45:562–6.
6. Udelson JE, Bacharach SL, Cannon RO, Bonow RO. Minimum left ventricular pressure during β-adrenergic stimulation in human subjects. Circulation 1990;82:1174–82.
7. Carroll JD, Hess OM, Hirzel HO, Krayenbuehl HP. Exercise-induced ischemia: the influence of altered relaxation on early diastolic pressures. Circulation 1983;67:521–8.
8. Mirsky I. Assessment of diastolic function: suggested methods and future considerations. Circulation 1984;69:836–41.
9. Craig WE, Murgo JP, Pasipoularides A. Evaluation of time course of left ventricular isovolumic relaxation in humans. In: Grossman W, Lorell BH, eds. Diastolic Relaxation of the Heart. Boston: Martinus Nijhoff, 1988:125–32.
10. Weiss JL, Frederiksen JW, Weisfeldt ML. Hemodynamic determinants of the time-course of fall in canine left ventricular pressure. J Clin Invest 1976;58:751–60.
11. Hess OM, Murakami T, Krayenbuehl HP. Does verapamil improve left ventricular relaxation in patients with left ventricular hypertrophy? Circulation 1986;74:530–43.
12. Paulus WJ, Sys SU, Nellens P, Heyndrickx GR, Andries E. Postextrasystolic potentiation worsens fast filling of the hypertrophied left ventricle in aortic stenosis and hypertrophic cardiomyopathy. Circulation 1988;78:928–40.
13. Paulus WJ, Heyndrickx GR, Buyl P, Goethals MA, Andries E. Wide-range load shift of combined aortic valvuloplasty-arterial vasodilation slows isovolumic relaxation of the hypertrophied left ventricle. Circulation 1990;81:886–98.
14. Inoue K. Percutaneous transvenous mitral commissurotomy using the Inoue balloon. Eur Heart J 1991;12(suppl B):99–108.
15. Abascal VM, Wilkins GT, Choong CY, et al. Echocardiographic evaluation of mitral valve structure and function in patients followed for at least 6 months after percutaneous balloon mitral valvuloplasty. J Am Coll Cardiol 1988;12:606–16.
16. Gorlin R, Gorlin SC. Hydraulic formula for calculation of area of stenotic mitral valve, other cardiac valves, and central circulatory shunts. Am Heart J 1951;41:1–29.

17. Fifer MA, Grossman W. Measurement of ventricular volumes, ejection fraction, mass, wall stress and regional wall motion. In: Grossman W, Baim DS, eds. Cardiac Catheterization, Angiography and Intervention. 4th ed. Philadelphia: Lea & Febiger, 1991:300–18.

18. Robinson TF, Cohen-Gould L, Remily RM, Capasso JM, Factor SM. Extracellular structures in heart muscle. In: Harris P, Poole-Wilson PA, eds. Advances in Myocardiology. New York: Plenum, 1985;5:243–55.

19. Nikolic S, Yellin EL, Tamura K, et al. Passive properties of canine left ventricle: diastolic stiffness and restoring forces. Circ Res 1988;62:1210–22.

20. Glower DD, Spratt JA, Snow ND, et al. Linearity of the Frank-Starling relationship in the intact heart: the concept of preload recruitable stroke work. Circulation 1985;71:994–1009.

21. Noble MIM, Milne ENC, Goerke JR, et al. Left ventricular filling and diastolic pressure-volume relation in the conscious dog. Circ Res 1969;24:269–82.

22. Weber KT. Cardiac interstitium in health and disease: the fibrillar collagen network. J Am Coll Cardiol 1989;13:1637–52.

23. Weber KT, Brilla CG. Pathological hypertrophy and cardiac interstitium: fibrosis and renin-angiotensin-aldosterone system. Circulation 1991;83:1849–65.

24. Covell JW. Factors influencing diastolic function: possible role of the extracellular matrix. Circulation 1990;81(suppl III):III-155–8.

25. Liu CP, Ting CT, Yang TM, et al. Reduced left ventricular compliance in human mitral stenosis: role of reversible internal constraint. Circulation 1992;85:1447–56.

26. Gash AK, Carabello BA, Kent RL, Frazier JA, Spann JF. Left ventricular performance in patients with coexistent mitral stenosis and aortic insufficiency. J Am Coll Cardiol 1984;3:703–11.

27. Gaasch WH, Folland ED. Left ventricular function in rheumatic mitral stenosis. Eur Heart J 1991;12(suppl B):66–9.

28. Koretsune Y, Corretti MC, Kusuoka H, Marban E. Mechanism of early ischemic contractile failure. Inexcitability, metabolite accumulation or vascular collapse? Circ Res 1991;68:255–62.

29. Ohtani M, Nikolic SD, Glantz SA. A new approach to in situ left ventricular volume clamping in dogs. Am J Physiol 1991;261:H1335–43.

30. Rousseau MF, Paulus WJ, Mengeot P, et al. Left ventricular relaxation in mitral stenosis before and after valvuloplasty (abstr). J Am Coll Cardiol 1989;13(suppl A):55A.

31. Pasipoularides A, Mirsky I, Hess OM, Krayenbuehl HP. Myocardial relaxation and passive diastolic properties in man. Circulation 1986;74:991–1001.